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IRON REGULATION BY FERRITIN(U) MASSACHUSETTS INST OF
TECH CAMBRIDGE FRANCIS BITTER NATIONAL MAGNET LAB
R B FRANKEL 15 AUG 87 N00014-85-K-0505

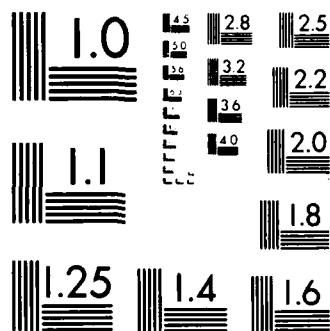
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<p>We are using Mossbauer spectroscopy and magnetic measurements in conjunction with electrochemical, pH and optical spectroscopic measurements to study the mechanisms of iron deposition and mobilization in mammalian and bacterial ferritin, and to study the structure of the iron containing core of these proteins.</p>			
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Iron Regulation by Ferritin
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Annual Report 7/1/86-6/30/87

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Project Goal

The goal of this project is to elucidate the mechanisms by which iron is deposited, stored and mobilized in ferritin proteins. This includes mechanisms of iron oxidation and reduction, and the relationship between iron deposition and mobilization and electron and proton flux.

Recent Accomplishments

Research over the past year has included study of iron deposited in bacterial ferritin from Azotobacter vinelandii, ferrous iron uptake by mammalian ferritin, and magnetic properties of multi-iron-oxo, hydroxo clusters that are synthetic analogues for the ferritin core. The results of these studies are summarized below.

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Research Summaries

1. Redox Properties and Mössbauer Spectroscopy of Azotobacter vinelandii Bacterial Ferritin

The bacterial ferritin obtained from Azotobacter vinelandii differs in significant ways from mammalian ferritin even though both proteins have a number of properties in common. AV ferritin has a high phosphate content ranging from near 0.5 to 1.0 P_i /core Fe, values much higher than that of 0.1 P_i /Fe reported for mammalian ferritin. The increased stability of the Fe^{2+} core, the different redox properties and the greatly different proton-uptake capability observed suggest a significantly different core character compared to that in mammalian ferritin. The high phosphate level in the core matrix thus seems to be the determining factor for these differences in core behavior.

The presence of heme in bacterial ferritin raises a number of questions regarding its purpose and its relationship with the core. The quite constant stoichiometry of 0.5 heme/subunit suggests a relationship of 1 heme being shared between two subunits but the significance of this possibility remains unclear.

Related to the reducibility of the AV ferritin core is the question of concerted proton transfer. We have previously reported that the reduction of mammalian ferritin core Fe^{3+} is accompanied by the transfer of $2H^+/e$. This proton transfer was determined directly from pH measurements and from the decrease in core Fe^{3+} reduction potential with decreasing pH. No such reduction potential variation with pH was encountered with AV ferritin, except at pH 6.0, suggesting the lack of proton involvement with core Fe^{3+} reduction. This demonstrates a significant difference between the core

properties of AV ferritin and mammalian ferritin, a result also suggested by the high P_i content of the former relative to the latter. If the AV ferritin is indeed the analogous iron storage protein in bacteria, the results so far obtained suggest the method of Fe storage and release may differ significantly from those in the mammalian system.

Mössbauer spectroscopy of oxidized AV ferritin indicates that the cores consist of antiferromagnetically-coupled high spin Fe^{3+} which exhibit superparamagnetic behavior at low temperatures. In this respect AV ferritin is similar to mammalian ferritin, except that the average blocking temperatures are less in AV ferritin. This might reflect the higher phosphate/ Fe^{3+} ratio and poorer crystallinity in AV ferritin. Reduction of AV ferritin results in Fe^{2+} in the core. Fe^{2+} and Fe^{3+} ions in partially reduced samples have different temperature dependences of their recoilless fractions, and different temperature dependences of their magnetic hyperfine interactions. Taken together with the apparent increase in the average Fe^{3+} particle size in the partially reduced samples, this suggests that Fe^{2+} ions form a separate phase in the AV ferritin cores, and that cores containing less iron atoms are preferentially reduced. The properties of reduced iron in AV ferritin are very similar to those of reduced iron in mammalian ferritin.

2. Binding of Fe^{2+} by Mammalian Ferritin

Strategies for the biological storage of iron in such a way that it is available for metabolic needs, net nontoxic, center on a widely distributed class of proteins, the ferritins. Ferritins are found in organisms as diverse as bacteria and mammals. Mammalian ferritin is a

roughly spheroidal, 120 Å diameter protein with a core of up to 4500 iron atoms in the 70 Å diameter interior cavity. The protein shell is composed of 24 nearly identical subunits that are arranged to isolate the iron-containing core from the cellular environment. Six hydrophilic and eight hydrophobic channels provide access to the protein interior, presumably for electrons, protons and iron ions, and other small ions and molecules.

The ferritin iron core is a hydrous ferric oxide phosphate with nominal formula $(\text{FeOOH})_8 (\text{FeO} \cdot \text{H}_2\text{PO}_4)_8$ and a structure similar to the protocrystalline mineral ferrihydrite, in which Fe^{3+} ions have six-fold oxygen coordination and oxygens are hexagonally close-packed. Iron is removed from the protein slowly by Fe^{3+} chelators and more rapidly by reductants and Fe^{2+} chelators. In the absence of chelators, the core can be reduced by up to one electron per iron atom, with all the reduced iron retained in the protein. Reduction is accompanied by the uptake of two protons from the external medium for every electron transferred to Fe^{3+} .

We have studied the binding of Fe^{2+} enriched to 90% in Fe-57 to holoferritin using Mössbauer spectroscopy. The experimental results can be summarized as follows: (a) Fe^{2+} binds to ferritin under anaerobic conditions; (b) the bound Fe^{2+} ions exchange electrons with the Fe^{3+} ions of the core; (c) the last added Fe^{3+} ions, those produced by oxidation of the originally added Fe^{2+} ions, are preferentially reduced when ferritin is incubated with a reductant such as dithionite.

The results imply that Fe^{2+} ions enter and are bound within the ferritin cavity. Since apoferritin binds ~12 Fe^{2+} ions per molecule, the binding of >100 Fe^{2+} ions by the holoprotein implies many more binding sites, perhaps on the surface of the core. Binding on the surface of the core would also facilitate the exchange of electrons with the Fe^{3+} ions of the

core. Since addition of Fe^{2+} ions produces a core that is spectroscopically indistinguishable from a core which is partially reduced electrochemically, redox states formed by partial reduction are thermodynamically as well as kinetically stable. Higher states of reduction, in contrast, may be only kinetically stable. The number of bound Fe^{2+} ions could depend on the average iron concentration per molecule, and because the reduction potential is pH dependent, on the pH of the medium.

3. Magnetic Properties of Oxo-bridged Trinuclear Iron (III) Complexes of a Polyimidazole Ligand

Oxo-bridged polyiron centers are widespread in the mineralogical and biological worlds. Discrete binuclear centers occur in the oxygen transport proteins hemerythrin found in marine invertebrates, in ribonucleotide reductase, and in purple acid phosphates. Polynuclear iron centers, found in the iron storage proteins ferritin and hemosiderin, are also involved in the formation of magnetic crystals in magnetotactic organisms and chitons. As discrete units, oxo-bridged trinuclear iron centers are thus far unknown in biology, but are likely intermediates in the formation of larger polynuclear iron aggregates. The $[\text{Fe}_3\text{O}]^{7+}$ unit has been proposed as the smallest building block of the ferritin core.

Two procedures were used for preparing the novel trinuclear complex $[\text{Fe}_3\text{O}(\text{TIEO})_2(\text{O}_2\text{CPh})_2\text{Cl}_3] \cdot 2\text{C}_6\text{H}_6$. An X-ray crystallographic study of this complex revealed an isosceles triangle of iron atoms with a triply bridging oxo atom nearly in the plane of the triangle. The structure of the $[\text{Fe}_3\text{O}]^{7+}$ core consists of two short Fe-O bonds and one long one. The coordinating spheres of the equivalent iron atoms, Fe(1) and Fe(2), are composed of two imidazole nitrogen atoms, the bridging oxo atom, a bridging

alkoxide oxygen atom of the TIEO^- ligand, an oxygen atom of a bridging benzoate ligand, and a terminal chloride ion. The two benzoate, two alkoxide, and μ -oxo groups bridge to Fe(3), which has a terminal chloride ligand to complete its coordination sphere. Two N-methylimidazole groups, one from each ligand, are not coordinated. From magnetization studies the ground state of $[\text{Fe}_3\text{O}(\text{TIEO})_2(\text{O}_2\text{CPh})_2\text{Cl}_3]$ is found to be $S = 5/2$, in contrast to the classical basic iron(III) carboxylates, which contain symmetrically bridged $[\text{Fe}_3\text{O}]^{7+}$ cores having $S = 1/2$. Variable temperature magnetic susceptibility measurements were fit to a theoretical expression derived from a spin Hamiltonian taking into account two different exchange pathways along inequivalent sides of the isosceles triangle. The analysis yielded $J_{12} = -55(1) \text{ cm}^{-1}$ and $J_{13} = J_{23} = -8.04 \text{ cm}^{-1}$, with the larger antiferromagnetic coupling interaction occurring between iron centers linked by the shortest μ -oxo bridge bonds. Mössbauer isomer shift and quadrupole splitting parameters at 4.2 K are $\delta = 0.48$ and 0.52 mm/sec and $\Delta E_Q = -1.16$ and 0.74 mm/sec for Fe(1) [= Fe(2)] and Fe(3), respectively. In external magnetic fields at 4.2 K there are two magnetic subsites with $H_{\text{hf}}(1) = H_{\text{hf}}(2) = 0$ and $H_{\text{hf}}(3) = -540 \text{ kOe}$, corresponding to Fe(1) and Fe(2) with local spin $|S_z\rangle = 5/2$. This result confirms the $|S_t = 5/2, S_p = 0\rangle$ ground state of the cluster. These results were compared and contrasted with structural, magnetic, and spectroscopic data for μ -oxodiiron(III), μ -hydroxodiiron(III), and symmetric μ_3 -oxotriiron(III) cores which, like the present asymmetric μ_3 -oxotriiron(III) core, are ubiquitous in mineralogy and biology.

4. Synthesis, Structure, and Properties of an Undecairon(III) Oxo-hydroxo Aggregate: An approach to the polyiron core in Ferritin

A novel, discrete undecairon(III) oxo-hydroxo aggregate, $[\text{Fe}_{11}\text{O}_6(\text{OH})_6(\text{O}_2\text{CPh})_{15}]$, has been synthesized by controlled hydrolytic polymerization in nonaqueous solvents of simple mononuclear and oxo-bridged binuclear ferric salts. The complex was structurally characterized in two crystalline forms. In the rhombohedral form, $[\text{Fe}_{11}\text{O}_6(\text{OH})_6(\text{O}_2\text{CPh})_{15}] \cdot 6\text{THF}$, the molecules have crystallographically required D_3 symmetry. The eleven-iron atoms define a twisted, pentacapped trigonal prism. Two type A iron atoms located on the threefold symmetry axis are joined by μ_3 -oxo bridges to six type B iron atoms at the corners of the twisted trigonal prism. These type B iron atoms are linked to one another and to three type C iron atoms, situated on twofold symmetry axes, by μ_3 -hydroxo bridges. A sheath of 15 bidentate bridging benzoate ligands, no two of which join the same pair of iron atoms, completes the pseudooctahedral coordination about each of the 11 high spin ferric centers. The Fe-O bond lengths range from 1.876 (5) Å for Fe-(μ -oxo) to 2.106 (8) Å for Fe-O(benzoate) type interactions. The six tetrahydrofuran molecules penetrate the sheath of benzoate ligands to form hydrogen bonds to protons on the six μ_3 -hydroxo ligands. The other crystalline form, $[\text{Fe}_{11}\text{O}_6(\text{OH})_6(\text{O}_2\text{CPh})_{15}] \cdot \text{H}_2\text{O} \cdot 8\text{MeCN}$, is triclinic and has no imposed molecular site symmetry. The molecular geometry of the undecairon(III) aggregate, however, is nearly identical with that in the rhombohedral form. Solutions of $[\text{Fe}_{11}\text{O}_6(\text{OH})_6(\text{O}_2\text{CPh})_{15}]$ in dry CH_2Cl_2 or CH_3CN are indefinitely stable, judging by optical spectroscopy. Cyclic voltammetric studies in the former solvent revealed a quasi-reversible one-electron reduction at $E_{1/2} = -0.309$ V vs. SCE, tentatively assigned to the formation of

$[\text{Fe}_{11}\text{O}_6(\text{OH})_6(\text{O}_2\text{CPh})_{15}]^-$, as well as two irreversible waves with peak currents at -0.817 and -1.323 V. The temperature-dependent magnetic susceptibility behavior of the undecairon(III) aggregate is consistent with a ground state spin $S_T = 1/2$ per aggregate and internal antiferromagnetic coupling. High-field magnetization and Mössbauer experiments reveal that the individual Fe_{11} molecules have incipient magnetic order with very low anisotropy and some exchange interactions on the order of 10 cm^{-1} . The presence of μ_3 -oxo, μ_3 -hydroxo, and carboxylate ligands, as well as the manner in which $[\text{Fe}_{11}\text{O}_6(\text{OH})_6(\text{O}_2\text{CPh})_{15}]$ self-assembles, make it an attractive model for the polyiron core in ferritin.

Projected Research

We have found that Mössbauer spectroscopy of ferritin formed by the addition of Fe^{2+} enriched in Fe-57 to apo- or holo-ferritin is particularly revealing. We are currently preparing a series of samples of mammalian and bacterial ferritin in which Fe^{2+} -57 is added to apo- or holo-ferritin from bacterial and mammalian sources. Some of these samples will be oxidized with subsequent additions of Fe^{2+} -56. In this way we plan to study the ferritin core from the nucleus of the core, through the middle layers, to the surface. Samples prepared at different pH values will shed light on the role of protons in core formation and structure.

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